The product of Boyce includes a dermal membrane that is covered with normal keratinocytes. The dermal membrane is prepared by freeze drying a second collagen gel on a first sponge which is also made by freeze drying. Therefore, Boyce relates to the preparation of two successive sponges. Such a structure is entirely different from that of the claimed invention. To make that difference more clear, claim 1 has been amended to more fully describe products of the invention.

There are two embodiments of the invention, one which includes a membrane resulting from the drying of a gel (referred to as a first embodiment) and one which includes a porous layer (referred to as a second embodiment). At the interview, it appeared clear that the Examiner recognized that the first embodiment of a membrane resulting from the drying of a gel was different from the surface collagen sponge of Boyce.

Only the second embodiment, which uses a collagen sponge, has some relevance with regard to Boyce. The Applicants' Representatives understood the Examiners' position as emphasizing that the use of the term "compressed" without any value was a relative term that did not provide a sufficiently distinctive feature over Boyce. Applicants understanding from the interview was that the proposed insertion of a compression pressure of at least about 50 bar would provide a sufficiently distinctive feature over Boyce.

It is indisputable that the formation of a sponge using compression at at least about 50 bar gives a resulting compressed sponge that is different than the resulting sponge of Boyce. Specifically, the compact collagen sponge of the claimed invention can be dense enough to impede the downward migration of surface deposited keratinocytes into the subdermal sponge.

Because Boyce does not have a product that contains a compact collagen membrane, Applicants assert that the disclosure of Boyce does not anticipate the Applicants' invention. Therefore Applicants respectfully request withdrawal of this rejection.

The Examiner rejected claims 9, 43, 53, and 54 under 35 U.S.C. § 102(b) as being anticipated by WO 91/16010 (Eisenberg).

Eisenberg requires the innoculation of commercially available cross-linked collagen sponges with cultured fibroblast cells (see page 8, from line 12 the three following paragraphs). After the fibroblast cells are incubated, to enable growth throughout the collagen matrix (page 8, before last paragraph first sentence), the sponge is inverted and the upper surface is laminated

with pepsine-treated, non-porous collagen (see page 8, last paragraph). It is disclosed by Eisenberg that the collagen gel is layered as a thin film onto the sponge and is incubated to complete polymerization of the collagen at 37°C for 60 minutes (page 9, last sentence of the first paragraph). Then, cultured keratinocytes are inoculated onto the laminate layer (page 9, first sentence of the second paragraph). Furthermore, the skin equivalent remains immersed in the culture medium throughout the incubation period (page 9, third paragraph). Prior to the clinical or in vitro application of the composite living skin equivalent, medium without bovine pituitary extract, is added to the culture medium (page 9, fourth paragraph).

In view of the above discussion, this document deals with a collagen gel surface layer, which is physically different from the film of collagen of the invention or of the compressed collagen sponge. It also results from the above discussion, that the Eisenberg composite material must always include cultured fibroblast cells and is not an acellular composite material as Applicants' invention is.

The acellular nature of the Applicants' invention is a significant advantage because the acellular composite material can be innoculated with living cells at any time, advantageously closer in time to the actual use of the product. The invention is therefore not limited to the prior inoculation of fibroblasts as is required by Eisenberg. Furthermore example 1, pages 13, of Eisenberg describes that a Vaseline gauze was placed over the cultured graft to facilitate the transporting and securing of the graft to the wound bed. This shows that the composite living skin is very fragile, contrary to the composite product of the invention.

In view of this, the Eisenberg reference does not anticipate Applicant's invention as claimed. Therefore, Applicants respectfully request withdrawal of this rejection.

Applicants would also like to point out that item 11 of the Office Action indicated that "no references were found teaching or suggesting claims 21 and 22, but they are rejected for other reasons". Therefore, because for the first embodiment of a collagen film resulting from the drying of a collagen gel, there is no prior art and for the second embodiment of obtaining a compact membrane by compressing a collagen sponge under a pressure of at least about 50 bar, which is held to be free of the prior art, the independent claims as now amended appear to be clearly allowable over the prior art.

Conclusion

In view of the amendments and comments presented herein, favorable reconsideration in the form of a Notice of Allowance is respectfully requested.

Respectfully submitted,

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Marked up version of Claims

1. (Twice Amended) A composite acellular product forming a collagen support comprising at least one porous collagen layer covered on at least one side with [an essentially] a compact collagen membrane selected from the group consisting of a collagen film prepared by drying a collagen gel and from a compressed collagen sponge prepared by a compression of a collagen sponge at a pressure of at least about 50 bar.

3. (Twice Amended) The product of claim 1, wherein the collagen of at least one of the porous layer and of the [essentially] compact membrane is selected from the group consisting of collagen and a mixture of collagen with a substance selected from the group consisting of a polysaccharide, a cellulose, dextran, an alginate and a carrageenan.

5. (Twice Amended) A composite product comprising the composite acellular product of claim 1, wherein at least one of the porous layer and of the [essentially] compact membrane, comprises living cells selected from the group consisting of normal living cells, genetically modified living cells and malignant living cells.

9. (Twice Amended) A composite product forming a collagen support comprising at least one porous collagen layer covered on at least one side with [an essentially] a compact collagen membrane selected from the group consisting of a collagen film prepared by drying a collagen gel and a compressed collagen sponge prepared by a compression of a collagen sponge at a pressure of at least about 50 bar, said porous layer comprising living fibroblasts and said [essentially] compact membrane comprising on the surface thereof living cells selected from the group consisting of keratinocytes, melanocytes, Merkel's cells originating from the blood, Langerhans' cells originating from the blood, sebocytes, cells originating from the blood, and nerve cells, the surface layer containing the living cells being cultivated while caused to emerge at the air-liquid interface of a compatible culture medium, while the porous layer containing the fibroblasts remains immersed during said cultivation step to give a reconstructed skin composed of a reconstructed dermis, comprising the fibroblasts having colonized the porous collagen layer

forming a three dimensional matrix, said dermis being covered with a multilayer epidermis comprising said collagen membrane.

12. (Twice Amended) The product of claim 1, wherein the [essentially] compact membrane is prepared prior to combination with the porous layer.

19. (Twice Amended) The product of claim 1, wherein at least one of the porous layer and compact [layer] membrane is produced from a collagen gel containing a mixture of soluble collagen and insoluble collagen, wherein the collagen is selected from the group consisting of type I collagen and type III collagen.

28. (Twice Amended) The process of claim 20, wherein at least one of the porous layer and compact membrane [layer], are crosslinked.

34. (Twice Amended) The process of claim 20, wherein living cells are introduced into at least one of the porous layer or compact membrane [layer].

61. (Amended) A composite product forming a collagen support comprising at least one porous collagen layer covered on at least one side with [an essentially] a compact collagen membrane selected from the group consisting of a collagen film prepared by drying a collagen gel and a compressed collagen sponge prepared by a compression of a collagen sponge at a pressure of at least about 50 bar, said porous layer comprising living cells and said [essentially] compact membrane comprising on the surface thereof living cells, the membrane surface [containing] comprising the living cells being cultivated while caused to emerge at the air-liquid interface of a compatible culture medium, while the porous layer [containing] comprises the [fibroblasts] living cells remains immersed during said cultivation step to give a reconstructed skin composed of a reconstructed dermis, comprising the living cells having colonized the porous collagen layer forming a three dimensional matrix, said dermis being covered with a multilayer epidermis comprising said collagen membrane.

64. (Amended) The product of claim 61, wherein said living cells on the surface of the membrane comprise keratinocytes [reconstructed dermis comprises the fibroblasts having

colonized the porous collagen layer forming a three dimensional matrix, said dermis being covered with a multilayer epidermis comprising said essentially compact collagen membrane].